09/971,776 ITW

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on April 6, 2005.

Doran R. Pace, Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322
Docket No. GJE-06FD3
Patent No. 6,809,082

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Aaron Gershon Filler, Andrew Michael Lindsay Lever
Issued	:	October 26, 2004
Patent No.	:	6,809,082 ✓
For	:	Synthetic Transfection Vectors

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction (in duplicate) for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Reads:**
Column 1, line 65: "non-degradable degradable gold"	Page 2, lines 14-15: --non-degradable gold--
Column 2, line 3: "to He"	Page 2, line 21: --to be--

J:\GJE\06FD3\Req.COC.doc/DNB/ems

Column 2, line 64: "four 10 hours."	Page 4, lines 9-10: --four hours.--
Column 3, line 14: "binding the attachment"	Page 4, lines 26-27: --binding protein. This pairing can be optimised by binding the attachment--
Column 3, line 23: "or 7.55"	Page 4, line 36: --of 7.5%--
Column 4, line 21: "stirring one hour"	Page 6, line 28: --stirring for one hour--
Column 4, line 35: "salts it aqueous"	Page 7, line 5: --salts in aqueous--
Column 4, line 42: "ribasomal"	Page 7, line 12: --ribosomal--
Column 4, line 47: "and a affinity"	Page 7, line 17: --and affinity--
Column 4, line 55: "gene or interest"	Page 7, line 25: --gene of interest--
Column 5, line 17: "destination"	Page 8, line 29: --destinations--
Column 5, line 25: "infection"	Page 8, line 37: --injection--
Column 5, line 52: "break sown"	Page 9, line 27: --break down--
Column 6, line 43: "of ddm_2O"	Page 11, line 12: --of ddH_2O--
Column 6, line 65: "$NaTO_4$"	Page 11, line 34: --$NaIO_4$--
Column 6, line 67: "sake"	Page 11, line 36: --shake--

Column 7, line 28: "NaBH"	Page 12, line 27: --$NaBH_4$--
Column 7, line 47: "particles **10** can"	Page 13, lines 9-10: --particles can--
Column 8, line 22: "herein"	Amendment dated October 23, 2002 (original claim 20) line 7: --wherein--.

A true and correct copy of pages 2, 4, 6-9, and 11-13 of the specification, as filed, and Applicants' Amendment Under 37 CFR §1.111 dated October 23, 2002 which supports Applicants' assertion of the errors on the part of the Patent Office accompanies this Certificate of Correction.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,

Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

DRP/ems

Attachments: Certificate of Correction in duplicate; copy of pages 2, 4, 6-9, and 11-13 of the specification
Copy of Applicants' Amendment dated October 23, 2002

new DNA as a sort of infection. The greatest progress has been made with a group of techniques in which DNA is coated onto gold colloid particles and the particles then subject to powerful electromagnetic fields in order to accelerate them to high speeds and so to hurl them against the cell walls of tissues. The particles plunge through the tissue surface and many viable DNA chains arrive inside the cell along with their non-degradable gold carrier. To reach tissues other than skin, a surgical operation is performed, and e.g. the tip of the liver is exposed and then a bombardment is carried out. This permits access only to surface layers of exposed tissues, is obviously injurious (since petechial haemorrhages immediately appear on the tissue surface), and deposits substantial amounts of non-degradable gold in the tissues.

In the method of this invention, the new DNA, RNA, plasmids, ribosomal particles, nucleic acid binding proteins and any other necessary molecules are caused to adhere to the outer surface of any one of a variety of metal oxide or mixed metal crystals of coated or uncoated type or to be attached to the surface of or included in the body of a variety of other types of biodegradable particles of appropriate size and capable of surface attachment to a cell adhesion molecule. These particles are in the size range of 5 to 100 nm in diameter including all attached coatings and other surface molecules. Included on the surface is one of a variety of nerve adhesion molecules or muscle adhesion molecules which bind to the surface of nerve and muscle cells, but preferably to muscle cells.

When such particles are constructed and then administered by routine percutaneous intramuscular injection, an exceedingly safe and efficient transfection process is initiated. The particles adhere to the outer surfaces of muscle cells and to the outer surfaces of the axon termini of motor nerve cells or preferably to the dendritic or sensory process of sensory axons within the muscle. After adherence, the particles are ingested into

muscular dystrophy or other diseases which particularly affect muscle or for treating diseases which affect neuromuscular transmission.

It must be noted, however, that such agents are sufficiently small that they can be safely injected intravenously. Because of their potentially hydrophilic coatings with e.g. dextran, the inventor has shown extended plasma half life for such agents with up to 25% of the initial injectate remaining in circulation for over four hours. This provides targeting access to a wide variety of cells in the blood marrow, circulating blood, and various glands and tissues. In all these cases, selection of appropriate targeting molecules for these particles will cause preferential adsorption to various useful cell types. While efficiency of phagocytosis of selectively adsorbed particles varies among tissues, there are a very wide variety of accessible intracellular sites. When the metal oxide core is constructed in such a way as to demonstrate superparamagnetism, then external magnetic fields (as from US 4,869,247) can be used to aid in targeting the agents.

In one example of synthesis of such compounds, the nucleic acid attachment to the particle is effected by specific nucleic acid binding proteins. A DNA plasmid or strand is constructed to include both the desired treatment gene and a segment with very high affinity for a selected nucleic acid binding protein. This pairing can be optimised by binding the attachment DNA segment to immobile latex particles using a cyanogen bromide immobilisation technique. Various nucleic acid binding proteins and other cell constituents are then passed through an affinity column made up to such DNA tagged latex particles. The specific fraction of nucleic acid binding protein is then eluted for use in making the particle.

A mixture of ferrous and ferric chloride salts is dissolved in a saturated dextran solution after the fashion of US 4,452,773 and precipitated by addition of 7.5% ammonia solution. The product is then moved into 0.1 M

The highly purified product of the second affinity step is now diluted in HEPES 20 mM pH 7.4, reconcentrated with Amicon Centriprep-100 or similar ultrafilters and then exposed to the genetic material to be delivered. When a mixed plasmid or strand is used, the binding protein interacts with the binding portion of the DNA and the large nucleic acid molecule carries with it the active gene of interest. It is also possible to use nucleic acid binding proteins which bind directly to a gene or segment of RNA or DNA of interest when such binding proteins are available.

The particles with bound DNA are passed through a Sephacryl column to clear unbound nucleic acid if desired and are now ready for concentration and dilution in an appropriate physiological solution for intramuscular injection. The agent is now injected into muscle whereupon natural processes of adhesion and endocytosis complete the gene transfection into the selected cell type.

In another example of the preparation, the initial precipitation of the iron salts is done by dropwise addition to ammonia solution without the presence of any coating dextran or other molecule. The resulting suspension is spun in a centrifuge at 500 g for 10 minutes and the pellet washed and resuspended in distilled water and the process then repeated but with a wash with 0.01N HCl. The resulting stable colloid is then exposed to a mixture of adhesion molecule protein, nucleic acid strands and/or nucleic acid binding proteins. After an incubation with gentle non-magnetic stirring for one hour, the remaining reactive sites on the particles are blocked by the addition of dextran or albumin protein. The particles are then passed through sephadex 150 and Sephacryl 200 columns then affinity purified by means of the cell adhesion molecule using for instance a column of affinity labelled agarose, sepharose, or latex beads.

In yet another example of the preparation, the initial precipitation is carried out by preparing a solution of very strong buffer such as 1 Molar or higher concentration

of HEPES or Tris at a pH of 7.4. The nucleic acids, any desired dextran, and or targeting proteins and nucleic acid binding proteins are added directly to this initial strong buffer. The mixture of dissolved ferrous and ferric iron salts in aqueous solution or in a solution containing dextran and/or protein and/or nucleic acids is then added dropwise to the buffer solution. In this fashion, the particles are formed in a rigidly buffered solution and so many fragile protein and peptide molecules can be used to form the particle coat where such molecules are necessary for targeting, for introducing ribonucleoprotein or ribosomal protein or other aspects of transcription signalling or actual transcription mechanism proteins along with the DNA or RNA. The product of this precipitation reaction is then further blocked with dextran or albumin if necessary, then purified with sephadex 150, sephacryl 200, Amicon ultrafilters and affinity columns as described above.

In yet another version of the synthesis, there is no nucleic acid binding protein used but only a cell surface adhesion molecule. Instead of the nucleic acid binding protein, a complementary fragment of the nucleic acid of interest is bound to the particles by a cyanogen bromide or other type of binding reaction or by adherence to an uncoated particle type. The gene of interest is then attached to the particle by its interaction with the bound complementary fragment after which purification steps are carried out as described above.

In summary, the present invention provides a synthetic transfection agent, the corresponding vector without the nucleic acid, and any combination of the components thereof. It will be appreciated that the synthetic transfection agent is based on precipitation of one of a variety of ceramic metal oxide particles similar in size to a virus. The metal oxide particle is coated with dextran or other biologically-tolerable polymer during the precipitation process. Chemically, the basic structure is similar to drugs in current use as magnetic resonance contrast agents.

The dextran or other coating of the particle is used as a framework to which various other types of molecules are then covalently bound. Typically, a targeting molecule such as an antibody or antibody fragment, or some other useful cell adhesion molecule is used. This causes the particle to adhere selectively to certain desirable cell types, e.g. a gp120 fragment to promote adherence to CD4 positive cells. In addition to the targeting molecule, it is also possible to attach a nucleic acid binding protein or short cDNA sequence to the dextran coat. In this fashion, particles can be produced with appropriate nucleic acid binding proteins and targeting molecules, and then subsequently loaded with the therapeutic DNA.

For intravascular administration, the particle size determines serum half-life and destination. Larger particles tend to be cleared into the reticuloendothelial cells by phagocytosis, while small particles achieve destinations determined more completely by their targeting molecule.

These particles can also be administered intramuscularly where they can gain entry into muscle cells and also can be ingested by nerve terminals in the muscle and subsequently subjected to axonal transport from the periphery towards the neural cell bodies in the central nervous system. In this fashion, mimicking the route of the Herpes virus, an intramuscular injection can be used to

deliver DNA across the blood-brain barrier for therapeutic purposes in selected regions of the nervous system. The axonal transport route also provides access to Schwann cells which line the axons.

It is further possible to provide the particles in aerosol form for pulmonary administration. A variety of other routes of administration are also feasible, including intravenous administration.

The particulate carrier is well suited for treating diseases involving the reticuloendothelial system through intravascular and inhalational routes, and to treat GI mucosal cells by enteral routes, as well as for intramuscular injection for access to muscle cells. Access via the intraneural route, to CNS and ganglion cells, is provided by intramuscular and intradermal injection.

It has been demonstrated that the particles are ingested by human macrophages, T-cells and osteogentic sarcoma cells, and that there is slow clearance of the particles from the blood stream in a rabbit, with 25% of the injected dose remaining in the circulation after four hours. Particles have coated with dextran and conjugated to both anti-CD4 and DNA polymerase as a nucleic acid-binding protein, with subsequent exposure to and uptake of DNA plasmids onto the particle surface. Particles may also be coated with DNA directly, rather than with dextran.

The particles are biodegradable in the sense that they can break down, in vivo, to materials that are essentially harmless. Thus, for example, while foreign materials such as gold particles may be found intact in cells years later, iron oxide particles dissolve readily into oxygen and iron, both of which are of course naturally present in abundance in cells and which then participate in normal cellular metabolism, storage and reuse. Iron poses some risk of toxicity when present in high amounts. The potential toxicity of ferrites is reduced by ensuring that they dissolve slowly, at a rate no faster than the cells' ability to process the elemental iron. Extension of the

washing steps. This apparently dissolves the iron in the hydrous oxides, but does not dissolve the well-formed ferrites. The result is a stable and uniform particle preparation with low toxicity (because it is a substantially pure ceramic preparation).

Example

Use double distilled water (not de-ionised) to make up the reaction mixture. The following steps are conducted:

Add 1.5 ml of 33% NH_3 to 4.5 ml of hot dH_2O (to make up 7.5% NH_4OH) and leave standing in a capped universal tube in the water bath and bring to 60°C.

Dissolve 1.25 g Dextran (MW 10,000) in 2.0 ml of ddH_2O then dissolve 225 mg $FeCl_3.6H_2O$ in the dextran solution. Alternatively, a trivalent lanthanide chloride may be substituted for 10 to 50% of the $FeCl_3$. When this is done, the subsequent post-reaction incubation is extended to two hours.

Dissolve 100 mg $FeCl_2.4H_2O$ in the Fe_3/dextran solution then place the mixture in a 60°C water bath for two minutes before starting to gradually add 6 ml of hot 7.5% NH_3 solution (60°C). The product is left to stand in the 60°C water bath for fifteen minutes.

The reaction product (dextran-coated ferrites) is spun at 1,000 g for 10 minutes and any precipitate is discarded. This process is repeated to complete three spins and the supernatant then applied to PD-10 columns equilibrated with 0.1 M NaAcetate buffer, pH 6.8 with 5 mM EDTA.

The black eluted fraction is diluted 1:3 with EDTA/Acetate buffer then concentrated to one-tenth the initial volume with Amicon Centriprep-100 ultrafilters. The retentate is then diluted 1:10 with EDTA/Acetate buffer then concentrated to a volume of 1.5 ml with the C-100 ultrafilters.

Add 0.30 ml of 20 mM $NaIO_4$ to the dextran ferrite solution (approx. 1.5 ml) while stirring then gently tumble or shake for 60 minutes at room temperature in the dark.

At the end of the 60-minute periodate incubation, the reaction is terminated by applying the reaction mixture to the PD-10 columns equilibrated with 20 mM borate buffer (pH 8.5).

An active site blocking solution is prepared using 100 mM $MnCl_2/CaCl_2$ for WGA binding reactions. Alternatively, e.g. calf thymus DNA can be used where the protein active site to be protected is on a nucleic acid binding protein.

Dissolve 10 mg of the protein (e.g. DNAse free DNA pol 1, Klenow fragment, integrase, useful proteins for subsequent translation steps, nucleic acid packaging protein and anti-CD4, WGA, or other cell-targeting protein) in 500 µl of 20 mM Na borate buffer, pH 8.5 at room temperature. The protein solution can be diluted to 12 ml with borate buffer, then concentrated with Centriprep-10 concentrators to remove DTT, glycerol, NaN_3 and other undesirable storage additives.

Add 10 µl of the blocking solution to the protein/borate solution then mix 2.0 ml of oxidised magnetite dextran with 500 µl of the protein/borate solution. Pipette 20 µl of the blocking solution into the 2.5 ml protein-dextran-magnetite mixture and mix well, then incubate for 6 to 18 hours at room temperature in a gentle tumbling or shaking device.

After the incubation, add 100 µl of 0.5 M glycine to the reaction mixture and incubate an additional 2 hours. Then add 250 µl of 0.25 M $NaBH_4$ to the magnetite-dextran-protein solution and allow to stand for 60 minutes, shaking periodically to release H_2 gas. At the end of the incubation, pass the reaction mixture through PD-10 columns equilibrated with 20 mM HEPES buffer, pH 7.4. Dilute the eluant 1:5 with HEPES buffer then concentrate with Centriprep-100 ultrafilters.

An affinity purification step is optional and detail is given for use with a WGA(lectin) targeting protein. Apply final retentate to affinity columns (20 mM HEPES), wash with HEPES, then carry out specific elution with 1 M

NAcGlu in HEPES buffer, pH 7.4. Pass the specific eluant through PD-10 columns equilibrated with HEPES to remove NAcGlu, Mn and Ca.

The desalted output is then diluted to a volume of 24 ml with HEPES buffer and concentrated with Centriprep-100 concentrators. The final retentate is sterilised by spinning at 500 h for one hour in 0.22 μm centrifugal microfilters.

The purified, sterilised synthetic vector particles can now be stored at 4°C for use within one to two weeks. They should not be frozen or lyophilised.

DNA adhesion with the DNA of interest can be done immediately prior to the transfection. The particle solutions are incubated with the DNA of interest with gentle tumbling or shaking for 6 to 24 hours.

Depending on the experimental or therapeutic protocol, the DNA-loaded vector solution may then be applied to cell cultures at a concentration of 1 mg/ml (approx. 5 mM Fe) of the synthetic vector (the final product of the preparation is 25 to 50 mg of synthetic vector). To assess efficiency, it may be compared to unadsorbed DNA solution. Alternatively, the DNA-loaded synthetic vector may be administered by IV or IM routes for in vivo use at 10 to 100 mM concentration. Non-precipitating magnetic-based separation techniques can be used to separate unbound DNA from particles. Where smaller DNA molecules are used, the separation can be done with Centriprep-100 concentrators.

COPY

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Assistant Commissioner for Patents
Washington, D.C. 20231 on October 23, 2002

Doran R. Pace, Patent Attorney

AMENDMENT UNDER 37 CFR §1.111
Examining Group 1635
Patent Application
Docket No. GJE-06FD3
Serial No. 09/971,776

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Brian A. Whiteman
Art Unit	:	1635
Applicants	:	Aaron Gershon Filler, Andrew Michael Lindsay Lever
Serial No.	:	09/971,776
Filed	:	October 4, 2001
Conf. No.	:	3171
For	:	Synthetic Transfection Vectors

Assistant Commissioner for Patents
Washington, D.C. 20231

AMENDMENT UNDER 37 CFR §1.111

Sir:

A Petition and Fee for a one-month Extension of Time through and including November 1, 2002, accompanies this Amendment.

In response to the Office Action dated July 1, 2002, please amend the above-identified patent application as follows:

In the Claims

Please cancel claims 1-17, without prejudice.

Please add the following new claims 18-23:

18. A gene delivery vector comprising ferrite particles having a polymeric coating to which a target polypeptide molecule, a nucleic acid and a nucleic acid binding protein are covalently bound.

19. A gene delivery vector according to claim 18 wherein said target polypeptide molecule is selected from the group consisting of wheat germ agglutinin, transferrin and nerve growth factor.

20. A gene delivery vector according to claim 18 wherein said target polypeptide molecule is an antibody or antibody fragment.

21. A gene delivery vector according to claim 18 wherein said polymeric coating is a dextran coating.

22. A gene delivery vector according to claim 18 wherein said ferrite particles are produced by the preparation of a mixture of ferrous and ferric chloride.

23. An injectable composition comprising a gene delivery vector according to claim 18 and a physiologically acceptable diluent.

Remarks

Claims 1-17 are pending in the subject application. By this Amendment, Applicants have canceled claims 1-17 and added new claims 18-23. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 18-23 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Support for the new claims can be found throughout the subject specification and in the claims as originally filed. New claim 18 refers to a gene delivery vector comprising polymer-coated ferrite particles, covalently bound to a target polypeptide molecule, a nucleic acid and a nucleic acid binding protein, the basis for which can be found, for example, at page 8, lines 12-24, of the subject specification. Support for new dependent claims 19 and 20, which refer to particular target polypeptides, can be found, for example, at page 5, lines 9 and 10, and page 8, lines 14-16, of the subject specification, respectively. Claim 21 is supported by the specification as a whole, including, for example, page 8, line 12. Support for claim 22 can be found, for example, at page 4, lines 34-37, page 6, lines 18-21, page 7, lines 4-7, and in the Example at page 11, lines 12-22, of the subject specification. New claim 23 is based on previous claim 15 and it is respectfully submitted that it is clear from the specification as a whole, such as the passages at page 8, line 25 through to page 9, line 15, that such a composition forms part of the invention.

Claim 16 is objected to under 37 CFR 1.75(c) as being of improper dependent form. As noted above, Applicants have canceled claim 16 by this Amendment. Accordingly, this rejection is now moot. Accordingly, reconsideration and withdrawal of the objection to the claim is respectfully requested.

Claims 1-17 are rejected under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention and as nonenabled by the subject specification. Applicants respectfully assert that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention and that the claims are enabled by the subject specification. However, in a sincere effort to expedite prosecution of the subject application to completion, Applicants have canceled claims 1-17 and submitted new claims 18-23. Applicants

respectfully assert that the new claims are directed to subject matter which the Examiner has indicated in the oustanding Office Action is supported and enabled by the specification (*i.e.*, a gene delivery vector comprising ferrite particles having a polymeric coating bound to a target polypeptide molecule, a nucleic acid and a nucleic acid binding protein, as indicated at pages 3 and 5 of the Office Action). Accordingly, reconsideration and withdrawal of the written description and enablement rejections under 35 USC §112, first paragraph, is respectfully requested.

Claims 1, 12, 13, 15, 16, and 17 are rejected under 35 USC §112, second paragraph, as indefinite. Applicants respectfully assert that the claims as filed are definite. However, by this Amendment, claims 1-17 have been canceled, thereby rendering this rejection moot. Applicants respectfully assert that the new claims obviate the grounds for rejection set forth in the outstanding Office Action. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph, is respectfully requested.

Claim 13 is objected to under MPEP 2173.05(h) on the grounds that the use of the term "and/or" is improper Markush group language. As noted above, claim 13 has been canceled. New claims 18-23 do not recite the term "and/or." Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 1-8, 11, 13, and 14 are rejected under the judicially created doctrine of "obviousness-type" double patenting over claims 1-4 of U.S. Patent No. 6,153,598. In addition, claims 1 and 15 are rejected under the judicially created doctrine of "obviousness-type" double patenting over claims 1-4 of U.S. Patent No. 6,153,598 in combination with U.S. Patent No. 4,826,823. Applicants respectfully assert that the claims are not obvious over the cited patents. However, in order to expedite prosecution of the subject application, Applicants have submitted a Terminal Disclaimer with this Amendment which obviates these rejections. Accordingly, reconsideration and withdrawal of the rejections is respectfully requested.

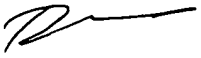
It should be understood that these amendments have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: 2421 N.W. 41st Street, Suite A-1
Gainesville, FL 32606-6669

DRP/sl
Attachment: Terminal Disclaimer

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Brian A. Whiteman
Art Unit	:	1635
Applicants	:	Aaron Gershon Filler, Andrew Michael Lindsay Lever
Serial No.	:	09/971,776
Filed	:	October 4, 2001
Conf. No.	:	3171
For	:	Synthetic Transfection Vectors

Assistant Commissioner for Patents
Washington, D.C. 20231

TERMINAL DISCLAIMER

Sir:

The owner, Syngenix Limited, of 100% interest in the above-identified patent application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173 as shortened by any terminal disclaimer, of prior Patent No. 6,153,598. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as shortened by any terminal disclaimer, in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer.

☒ I am the attorney of record.

☒ I authorize the Patent Office to charge the amount of ☒ $55.00 (small entity) ☐ $110.00 (large entity) for the terminal disclaimer fee under 37 CFR 1.20(d) to Deposit Account No. 19-0065.

October 23, 2002
Date

Doran R. Pace
Patent Attorney
Reg. No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: 2421 N.W. 41st Street, Suite A-1
Gainesville, FL 32606-6669

DRP/sl

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,809,082

DATED : October 26, 2004

INVENTORS : Aaron Gershon Filler, Andrew Michael Lindsay Lever

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,
Line 65, "non-degradable degradable gold" should read --non-degradable gold--.

Column 2,
Line 3, "to He" should read --to be--.
Line 64, "four 10 hours." should read --four hours.--.

Column 3,
Line 14, "binding the attachment" should read
--binding protein. This pairing can be optimised by binding the attachment--.
Line 23, "or 7.55" should read --of 7.5%--.

Column 4,
Line 21, "stirring one hour" should read --stirring for one hour--.
Line 35, "salts it aqueous" should read --salts in aqueous--.
Line 42, "ribasomal" should read --ribosomal--.
Line 47, "and a affinity" should read --and affinity--.
Line 55, "gene or interest" should read --gene of interest--.

Column 5,
Line 17, "destination" should read --destinations--.
Line 25, "infection" should read --injection--.
Line 52, "break sown" should read --break down--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

PATENT NO. 6,809,082

No. of additional copies

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,809,082

DATED : October 26, 2004

INVENTORS : Aaron Gershon Filler, Andrew Michael Lindsay Lever

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 6,
Line 43, "of ddm_2O" should read --of ddH_2O--.
Line 65, "$NaTO_4$" should read --$NaIO_4$--.
Line 67, "sake" should read --shake--.

Column 7,
Line 28, "NaBH" should read --$NaBH_4$--.
Line 47, "particles **10** can" should read --particles can--.

Column 8,
Line 22, "herein" should read --wherein--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950